

REMARKS

All formality issues raised in the Office Action are overcome by the amendments to the form of the claims.

The only issue that is not addressed by the amendments is raised in point viii) of the Office Action, under section 112, second paragraph, where it is alleged that it is unclear who the subject is that needs prevention of infection and how one can say whether the infection is prevented.

The prevention of infections per se, e.g., of tuberculosis (see, for example, claim 12), or of mycobacterial infections (see, for example, claim 10) or of other bacterial infections (see, for example, claims 14 and 15), are common in the pharmaceutical arts.

As support, attached is a printout of a table titled "Drugs Given to Prevent Infections" printed in the Blood & Marrow Transplant Newsletter, Issue # 19, Vol. 4, No. 5, September 1993, authored by G. Yee and D. L. Stanley. The table extends through six pages and identifies compounds by generic and trade names and groups them into various classes, e.g., antibiotics, antifungals, antivirals, etc.

Also attached are two abstracts, i.e., Ji B. et al., Effectiveness of rifampin, rifabutin, and rifapentine for preventive therapy of tuberculosis in mice, *Am Rev Respir Dis.* 1993 Dec;148(6 Pt 1):1541–1546 and Chapuis, L. et al., Preventive therapy of tuberculosis with rifapentine in immunocompetent and nude mice, *Am. J. Respir. Crit. Care Med.* 150:1355-1362.

All of these references clearly demonstrate that the prevention of infections per se of various types, including of tuberculosis, which is caused by a certain type of mycobacteria, has been known by those of ordinary skill in the art for a long time prior to the filing date of the present application. Thus, one of ordinary skill in the art would know the scope of what is claimed; and thus, the indefiniteness rejections are not warranted.

One of ordinary skill in the art, for example, would know that prevention of infections is desirable at most times by most people, and especially in certain settings and on subjects at high risk, e.g., healthcare workers or caregivers exposed to various infectious agents, to persons with depressed immune systems, e.g., HIV patients often develop tuberculosis, high risk populations who may be or have been exposed to tuberculosis or various respiratory bacterial infections (for example, in the case of an outbreak), burn victims, persons undergoing operations, immunosuppressed persons with a history of exposure and those with


evidence of serum conversion (tuberculosis antigens are found, although the disease is not yet broken out), etc. Prevention of infections can be and has been practiced by those of ordinary skill in the art using other agents. This alone rebuts the Examiner's concerns.

Additionally, applicants teach that the "compounds of the invention have a higher anti-mycobacterial activity than known tuberculosis agents, especially rifampicine, " and that "they additionally show anti-microbial activity against ordinary bacteria." See page 2, lines 3-5. These teachings are confirmed by data presented in the specification. See examples 6 and 7, and the results thereof in tables 1 and 2.

Reconsideration is respectfully requested.

The Commissioner is hereby authorized to charge any fees associated with this response or credit any overpayment to Deposit Account No. 13-3402.

Respectfully submitted,



Csaba Henter, Reg. No. 50,908
Anthony J. Zelano, Reg. No. 27,969
Attorneys for Applicants

MILLEN, WHITE, ZELANO
& BRANIGAN, P.C.
Arlington Courthouse Plaza I
2200 Clarendon Boulevard, Suite 1400
Arlington, Virginia 22201
Direct Dial: 703-812-5331
Facsimile: 703-243-6410

Filed: February 14, 2007

K:\GULDE\52\REPLY FEB 07.DOC

Am Rev Respir Dis. 1993 Dec;148(6 Pt 1):1541-6.

Related Articles, Links

Effectiveness of rifampin, rifabutin, and rifapentine for preventive therapy of tuberculosis in mice.

Ji B, Truffot-Pernot C, Lacroix C, Raviglione MC, O'Brien RJ, Olliaro P, Roscigno G, Grosset J.

Faculte de Medecine Pitie-Salpetriere, Paris, France.

To identify alternative regimens for preventive therapy of tuberculosis, the pharmacokinetics and antimicrobial activities of rifampin (RMP), rifabutin (RBT), and rifapentine (RPT) were compared in BCG-vaccinated and *M. tuberculosis*-infected immunocompetent mice. RPT showed the highest serum peak level (C_{max}) and the longest half-life (t_{1/2}), whereas RBT displayed the lowest C_{max} and the shortest t_{1/2}. On weight-to-weight basis, both RPT and RBT were more bactericidal than RMP. The activity of RMP was significantly reduced when the frequency of administration was reduced from six to three times weekly, whereas significant bactericidal activity was still observed in mice treated with RPT, 10 mg/kg up to once fortnightly, or RBT, 10 mg/kg twice weekly. Because the bactericidal activity of RBT, 10 mg/kg six times/wk for 6 wk, or RPT, 10 mg/kg two times/wk for 12 wk, was comparable to that of RMP, 10 mg/kg six times/wk for 12 wk in mice, the two regimens are appropriate for clinical trials of preventive therapy of tuberculosis.

Am. J. Respir. Crit. Care Med., Vol 150, No. 5, Nov 1994, 1355-1362.

Preventive therapy of tuberculosis with rifapentine in immunocompetent and nude mice

L Chapuis, B Ji, C Truffot-Pernot, RJ O'Brien, MC Raviglione and JH Grosset
Faculte de Medecine, Pitie-Salpetriere, Paris, France.

The effectiveness of intermittent administration of rifapentine (RPT), with or without isoniazid (INH), for preventive therapy of tuberculosis was evaluated in immunocompetent (normal) and nude mice. After infection with a small inoculum of *Mycobacterium tuberculosis* H37Rv, normal mice developed a chronic and nonfatal infection, and the bacterial population became relatively stable after an initial period of limited multiplication. On the other hand, nude mice developed an acute and fatal infection, and all untreated mice died within 5 wk, with very high colony-forming-unit (CFU) counts in their organs. Various degrees of bactericidal activity were shown in normal mice after daily treatment with rifampin (RMP) plus pyrazinamide (PZA) for 13 wk, INH daily for 26 wk, or RPT once weekly for 13 or 26 wk or once fortnightly for 26 wk. The activity of RPT was significantly enhanced when INH was added at the same dosing frequency. In nude mice the response of *M. tuberculosis* infection to certain regimens was less favorable than that in normal mice, suggesting that preventive therapy may be less effective in severely immunodeficient hosts even during treatment. After chemotherapy was stopped, virtually all nude mice relapsed within 12 wk regardless of the regimen administered, whereas no or very few relapses were observed in normal mice that had been treated with RMP+PZA daily for 13 wk, or RPT alone or RPT+INH once weekly for 26 wk. The latter three regimens and RPT+INH once weekly for 13 wk may be applied for fixed-duration preventive therapy in human immunodeficiency virus (HIV)-negative subjects. (ABSTRACT TRUNCATED AT 250 WORDS)



Blood & Marrow Transplant Newsletter



Issue #19
Vol. 4, No.5

September 1993

Preventing
Infections

Drugs Given
to Prevent
Infections

Someone
You Should
Know



News Bits



Gift Cards

Drugs Given to Prevent Infections

By Gary Yee Pharm D and Denise L Stanley Pharm D.

Generic Name	Trade Name	Route Given	Common Side Effects
Antibiotics			
Amikacin	Amikin	IV or oral	Diarrhea, change in kidney function or hearing.1
Ampicillin/clavulanic acid	Augmentin	oral tablet oral liquid	N/V/D, GI upset, rash, change in liver function.
Aztreonam	Azactam	IV or oral	Allergic reactions, rash, N/V/D, change in liver function.
Cefoperazone	Cefobid	IV	Allergic reactions, rash, N/V/D, bleeding problems, vein irritation.
Cefotaxime	Claforan	IV	As above, except for bleeding problems.
Ceftazidime	Fortaz, Tazidime	IV	As above, and change in kidney function.
Ciprofloxacin	Cipro	oral tablet, IV	GI upset, N/V/D, headache, change in kidney or

			liver function. Caution in age < 18. Drug interactions.
Colistin Sulfate or Polymixin E	Colymycin S	oral liquid	N/V/D, GI upset.
Gentamicin	Garamycin	IV or oral	Diarrhea, change in kidney function(1) or hearing (1), muscle weakness. (1)
Imipenem/cilastatin	Primaxin	IV	Allergic reactions, rash, vein atation, N/V/D, seizures, change in kidney function.
Metronidazole	Flagyl	oral tablet, IV	N/V/D, GI upset, metallic taste, change in liver function. Avoid alcohol. Discolors urine.
Mezlocillin	Mezlin	IV	Allergic reactions, rash, N/V/D, bleeding problems or decreased blood counts, change in kidney or liver function.
Neomycin	Mycifradin	oral tablet	GI upset N/V/D, rash, change in kidney function. (1)

Norfloxacin	Noroxin	oral tablet	Headache, dizziness, nausea, change in liver or kidney function. Caution in age < 18.
Ofloxacin	Floxin	oral tablet, IV	GI upset, diarrhea, insomnia, headache, dizziness. Caution in age < 18.
Penicia V K+	Veetids Pen Vee K	oral tablet oral liquid/IV	Skin rash, GI upset, diarrhea, fever.
Piperacillin	Pipracil	IV	Same as above, under mezlocillin.
Polymixin B	Aerosporin	oral liquid	N/V/D or GI upset.
Rifampin	Rifadin, Rimactane	oral capsule	Reddish discoloration in urine, stool, tears, sweat; N/V, flu-like symptoms, rash, change in liver function. Drug interactions.
Ticarcillin or Ticarcillin/clavulinate	Ticar Timentin	IV	Same as above, under mezlocillin.
Tobramycin	Nebcin	IV or oral	Same as above, under mezlocillin.
Trimethoprim/ Sulfamethoxazole or TMP/SMX	Bactrim, Bactrim DS Septra	oral tablet or IV	N/V/D, GI upset, rash, decreased blood counts, change in kidney or liver

			function.
Vancomycin	Vancoled Vancocin	oral capsule, oral liquid, IV	Allergic reactions, rash, vein irritation, change in kidney function or hearing, decreased white blood cell count, stomach upset.
Antifungals			
Amphotericin B	Fungizone	liquid, IV, nasal spray, mouthrinse	N/V/D, metallic taste, change in kidney function, change in electrolytes, rash, fever, severe allergic reactions, anemia.
Clotrimazole	Mycelex	oral troches	N/V, change in taste, change in liver function. (1)
Fluconazole	Diflucan	oral tablet, IV	N/V/D, rash, change in liver function, drug interactions.
Itraconazole	Sporonox	oral capsule	N/V/D, change in liver function, drug interactions.
Ketoconazole	Nizoral	oral tablet	N/V/D, headache, dizziness, rash, change in liver function, food and

			drug interactions.
Nystatin	Nilstat, Mycostatin	oral liquid	GI upset, N/V/D, change in taste.
Antivirals			
Acyclovir	Zovirax	oral capsule, oral liquid/IV	Diarrhea, dizziness, rash, fatigue, change in kidney function, vein irritation, confusion, change in liver function.
Ganciclovir/DHPG	Cytovene	IV	Decreased white blood cells, anea fever, rash, change in liver function.
Foscarnet	Foscavir	IV	Headache, fatigue, nausea, fever, change in kidney function, change in electrolytes.
Antiprotozoals			
Pentamidine	Pentam	Inhalation or IV	Decreased blood pressure, rash, N/V, decreased blood counts, change in kidney or liver function.
Trimethoprim/Sulfamethoxazole or TMP/SMX	Bactrim, Septra,	oral tablet or IV	Same as above, under antibiotics.

		Septra DS		
Tropical/Other				
Chlorhexidine	Peridex	oral rinse	Metallic taste, N/V, staining of teeth, minor oral irritation, allergic reactions. (1)	
IVIG	Sandoglobulin Gammagard PolyGam Cytogam	IV	Fever, chills, allergic reactions, rash.	
Abbreviations:				
N=nausea,	V = vomiting	D = diarrhea		
1= not commonly seen at the dose used for prophylaxis	2= affected by multiple foods; should be taken with orange juice or other acidic foods			

◀ Archive ▲ Top Next ▶
Someone You Should Know